REMARKS/ARGUMENTS

Rejection Under 35 USC 103

Claims 82-87 and 91-100 have been rejected under 35 USC 103(a) over Mouritsen et al. (WO 95/05849) in view of van der Zee et al. (Vaccine Vol. 13, No. 8, pages 753-758, 1995). More specifically, the Patent Office states:

> ...it would have been obvious to one of ordinary skill in the art...to modify ubiquitin fusion proteins disclosed by Mouritsen et al. to use GnRH as the self epitope as disclosed by van der Zee et al. since GnRH is considered the pivotal regulatory peptide in mammalian reproduction and there is a demand for an effective, low cost means of controlling fertility in domestic animals. The resulting fusion protein would benefit from the increased stabilization, increased efficiency of translation and increased preservation of biological activity due to proper folding associated with ubiquitin fusion proteins, as well as the increased efficacy associated with the use of the GnRH self antigen.

Applicant respectfully traverses this rejection. Applicant submits that the motivation for the proposed combination of Mouritsen et al. in view of van der Zee is lacking. Applicant notes that MPEP 2143.01 states:

> Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. 'The test for an implicit showing is what the combined teachings , knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.' *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

Mouritsen et al. teach the incorporation of one or more T-cell epitopes into the highly conserved self-protein ubiquitin. Mouritsen et al. disclose one ubiquitin fusion protein containing the T-cell epitope ovalbumin (OVA 325-336) and another containing the T-cell epitope HEL 50-61. van der Zee et al. teach a fusion protein containing GnRH fused to the T-cell epitope *P.*

fimbriae. In both references cited, foreign epitopes are essential elements in the fusion proteins for generating immune responses. A protein fusion resulting from the combination of ubiquitin and any self epitope(s) is neither implicitly nor explicitly suggested. Applicant disagrees that the motivations cited by the Patent Office would be sufficient to arrive at Applicant's invention since both references, as well as the state of the art at the time of Applicant's filing, suggest that the claimed combination would not generate an immune response.

Prior to the present invention, ubiquitin fusions were not recognized in the art as being immunogenic for self-epitopes fused to ubiquitin protein. One of skill in the art would not have expected ubiquitin fusions to generate an immune response to a self-epitope in a protein fusion since ubiquitin itself is highly conserved. Prior to Applicant's discovery, protein fusions of highly conserved proteins with self-proteins were not recognized as immunogenic. As the Patent Office notes, Mouritsen et al. disclose that "the antibody response induced is not necessarily restricted to the inserted T-cell epitope (page 6, lines 33-35)."

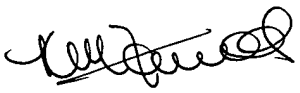
Applicant submits that the recognition of the ability of a fusion protein to generate antibodies to ubiquitin is not a disclosure or suggestion that a ubiquitin fusion with a self-protein is immunogenic. Mouritsen et al. does not disclose nor suggest the immunogenic property of ubiquitin fused to a self-epitope. Rather, the teachings of Mouritsen et al. suggest that a T-cell epitope is able to generate antibodies to the ubiquitin self-epitope. Since the inherent immunogenic property of a ubiquitin fusion was not recognized prior to Applicant's discovery, Applicant submits that the motivation to combine ubiquitin in a fusion with a self-epitope(s), wherein the ubiquitin fusion is immunogenic for the non-ubiquitin self-epitope(s), is therefore lacking. As a result, Applicant submits that the rejected claims are nonobvious over the combination of the cited references. Mouritsen et al. and van der Zee et al. are clear examples in the art of methods for stimulating an immune response providing protein fusions comprising

self-proteins with non-self proteins, wherein the non-self proteins are immunogenic for the self-proteins. Applicant submits that Claims 82-87 and 91-100 of the instant application claim profoundly different methods for stimulating an immune response, methods which include providing a ubiquitin fusion protein comprising ubiquitin fused to epitope-containing segments comprising non-ubiquitin self-epitopes, wherein the ubiquitin fusion is immunogenic for the non-ubiquitin self-epitopes.

Summary

In light of the above amendment, consideration of the subject patent application is respectfully requested. Any deficiency or overpayment should be charged or credited to Deposit Account No. 500282.

Respectfully submitted,



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